

REMARKS

Claims 1-22 are pending. Applicants acknowledge the election of Group I. Claim 1 has been amended to include the following proviso above the second-to-last line, after "heteroatom;" and before "or a pharmaceutically", the following language has been inserted: " provided that R<sub>b</sub>, R<sub>d</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>, if halo, are chloro;". "Halo" is defined in the specification at page 6, lines 30 and 31, as "fluoro, chloro, bromo, and iodo, and preferably fluoro or chloro." Support for the preference for chloro is found herein. No new matter is believed to have been added.

Reconsideration of the pending claims is respectfully requested in view of the remarks below and the above amendment.

35 USC 112, first paragraph

Claims 1-17 and 20, 21 were rejected under 112, first paragraph, because "the specification, while being enabling for preparation and use of compounds wherein R<sub>3</sub> is hydrogen or methylsulfonyl, W is O or O-R<sub>9</sub>, Z is nitrogen-containing heterocycle or NR<sub>11</sub>R<sub>12</sub>, does not reasonably provide enablement for preparation and use of compounds wherein R<sub>3</sub>, W, and Z are other than those functional groups specified above [...]". This rejection is respectfully traversed.

It is well-established that Applicants must satisfy the enablement requirement by teaching one of ordinary skill how to make and use the claimed invention. If the Office Action is suggesting that synthesis for every possible compound or combination be exemplified, that suggestion is inconsistent with established law.

First, Applicants have provided a wealth of information and guidance to assist one of ordinary skill in preparing the claimed compounds. The present specification provides synthetic guidance on pages 12 through 20, including 11 synthetic schemes. In addition, there are 17 detailed Examples of a wide variety of compounds. This is more than enough guidance and information for a person of ordinary skill to prepare the claimed compounds.

Second, Applicants' claims are relatively narrow. For example, Applicants have exemplified R3 as hydrogen and methylsulfonyl; Applicants also claim other alkylsulfonyls, phenylsulfonyl, and certain related groups such as alkylcarbonyls for R3.

In short, one of ordinary skill would be able to prepare the claimed compounds using the guidance, schemes, and detailed examples provided in the specification.

The Office Action also asserted that "the instant specification provides no direction or guidance for how to use the disclosed (and claimed) compounds ..." (Office Action, page 4). This rejection is respectfully traversed.

First, on pages 44 and 45 of the specification, Applicants have presented biological protocols which clearly teach one of ordinary skill to identify compounds that have H3 antagonist activity. These are straightforward transfection and binding assay experiments whose principles and technical manipulations are entirely familiar to those in the art. Furthermore, the nexus between H3 antagonist activity and various claimed diseases or conditions is taught, for example, in the Background section on pages 1 and 2 of the specification, citing various peer-reviewed papers and patent publications.

Second, the detailed Examples also provide H3 activity data for the exemplified compounds which are representative of the claimed scope of the invention.

This is all that is required to satisfy enablement. For the reasons stated above, Applicants submit that the claimed invention is fully enabled and respectfully request that this rejection be reconsidered and withdrawn.

35 USC 112, second paragraph

Claims 1, 9 and 12-18 were rejected under 112, second paragraph, as indefinite. This rejection is respectfully traversed.

First, the Office Action stated that "heterocyclyl" or "heterocyclic" was indefinite. Applicants respectfully draw attention to the definitions on page 6, lines 16-21, and the examples of heterocyclic radicals provided on page 6, lines 22-29 in the specification, as well as throughout the disclosure in the detailed examples and lists of compounds.

Second, claims 1, 18, 19, and 22 were viewed as indefinite "because the metes and bounds of 'ester' and 'amide' were unknown" (Office Action, page 5). Esters and amides are known to those of skill in the art. In addition, ester is defined generally, for example, at page 26, lines 15 through page 27, lines 20 page; and more specifically at page 23, lines 27 through 29. Amides are defined generally, for example, at page 29, lines 14-33. Preferred amides are described at page 23, lines 26-27, in the specification.

In view of the above multiple definitions of varying scope, as well as the detailed examples throughout the specification,

Applicants respectfully request that the rejection of claims 1, 9, 12-19, and 22 for indefiniteness be withdrawn.

35 USC 102

Claims 1, 2, 8, 10-16, 20 and 21 were variously rejected for anticipation.

Claims 1, 2, 8, 10-16, 20, and 21 were rejected for anticipation by Chirgadze et al. (WO 98/48797).

The Office Action did not state a specific example that anticipated Applicants' claims. However, based on the breadth of Chirgadze's generic claim 1, Chirgadze cannot anticipate Applicants' invention. For example, in Chirgadze's claim 1, R<sup>1</sup> is a para-substituent on a phenyl where:

[...]R<sup>1</sup> is carboxy, [(1-4 C) alkoxy]carbonyl, hydroxymethyl, or -X<sup>1</sup>-(CH<sub>2</sub>)<sub>s</sub>-NR<sup>s</sup>R<sup>t</sup> in which X<sup>1</sup> is a direct bond, methylene or O; s is 1 or 2; provided that when s is 1, then X<sup>3</sup> is a direct bond; and R<sup>s</sup> and R<sup>t</sup> are independently hydrogen, or (1-3C)alkyl or the group NR<sup>s</sup>R<sup>t</sup> is pyrrolidino, piperidino, or morpholino; [...]

(Chirgadze, page 49). Chirgadze requires that R<sup>1</sup> be one of the above 4 groups. The position in Applicant's claim 1 corresponding to Chirgadze's R<sup>1</sup> is the substitution available on Z' when Z' is phenyl. The substitutions available to Z' (see claim 1, page 48, lines 8-11 relating to optional substitutions, namely alkyl, alkoxy, halo, hydroxy, phenyl, and phenylalkyl) do not include any of Chirgadze's required groups.

In view of the above, Applicants respectfully request that the rejection over Chirgadze be withdrawn.

Claims 1, 2, 8, 10-16, 20, and 21 were rejected under 35 USC 102 (b) in view of Neuenschwander (US 5,385,912), citing examples in Column 31. This rejection is respectfully traversed.

Column 31 provides possibilities for moiety Z, and is part of Table VI, the relevant part of which provides a general structure at the top of columns 25 and 26. This generalized structure is a bridged bicyclic compound with a Z-substituted benzyloxy group. In fact, claim 1 of this reference requires that moiety "A" be a bridged bicyclic group (see column 43, lines 1-10). In other words, the Office Action draws attention to compounds requiring a bridge bicyclic core. However, there are no bridged bicyclic groups claimed in Applicants' claim 1. For this reason, Applicants respectfully request that this rejection over Neuenschwander be reconsidered and withdrawn.

Claims 1, 2, 8, 10-16, and 20 and 21 were rejected over Connor (WO 98/06703), citing examples on page 24. This rejection is respectfully traversed.

Connor's claim 1 requires that  $R_7$  be  $(CH_2)_nNR_{10}R_{11}$  where  $n$  is 2 to 6 and where  $R_{10}$  and  $R_{11}$  are each lower alkyl or together can form a ring (generic on page 50, definitions on page 51, line 24 through page 52, line 5). It is not possible to form Connor's  $(CH_2)_{0-3}-NR_6R_7$  moiety as required by Connor, because there is no equivalent to Connor's required  $R_7$  moiety in Applicants' claim 1. For example, compare Connor's  $(CH_2)_{0-3}-NR_6R_7$  moiety to Applicants' moiety  $R_c$ , where  $R_c$  is  $WZ$ .  $W$  can be alkylene, and  $Z$  is  $NR_{11}R_{12}$ . However, neither  $R_{11}$  nor  $R_{12}$  can be the equivalent of Connor's  $R_7$  (see Applicants' claim 1, page 48, lines 2-6).

In view of the above, Applicants respectfully request that this rejection over Connors be reconsidered and withdrawn.

Claims 1, 8, 10, 12 and 26 were rejected as anticipated by Agarwal. This rejection is respectfully traversed.

There are three structures shown in CA 115:49618. The first and third structures do not have a 5,6 fused bicyclic structure as required by Applicants' claim 1. The second structure requires a para-chloro-substituted benzoyl (or phenylcarbonyl). Applicants do not claim a benzoyl at that position. In view of the above, Applicants respectfully request that this rejection over Agarwal be withdrawn.

Claims 1, 2, 8, 10, 12-16, 20 and 21 rejected as being anticipated by Joshi. This rejection is respectfully traversed in part and overcome in part by amendment.

There are three structures shown in CA 105:190834. In the first structure, neither R1 nor R2 satisfy the requirement in Applicants' claim 1 for a "WZ" moiety, as defined on page 47, line 27 through page 48, line 12. The second and third structures shown were contained in Applicants' claims as filed. However, claim 1 has been amended to require that Rb, Rd, R5, R6, R7, and R8 cannot be fluoro. Based on the abstract, the presence of fluoro is apparently critical for the anti-fertility activity of Joshi's compounds. Avoiding fluoro therefore overcomes both the novelty rejection and any future rejection for obviousness, since these fluoro substitutions are apparently central to Joshi's teaching.

In view of the above, Applicants respectfully request that this rejection over Joshi be withdrawn.

In summary, none of the cited art anticipates Applicants' invention as amended.

35 USC 103

Claims 1, 2, 8, 10-16, 20 and 21 were rejected as unpatentable over the combination of Chirgadze, Neuenschwander, and Connor.

For the reasons stated above, Chirgadze, Neuenschwander, and Connors do not disclose the claimed invention.

First, there is no motivation to combine these references. Chirgadze relates to "thrombin inhibitors, coagulation inhibitors, and thromboembolic" agents (Abstract). Neuenschwander's compounds are stated to be useful for reducing levels of serum cholesterol in the body without significantly reducing mevalonic metabolite synthesis (Abstract). Connor relates to MCP-1 antagonists useful in the treatment of inflammation, arteriosclerosis [sic], restenosis, and immune disorders such as arthritis and transplant rejection (Abstract). These are distinct processes or utilities and the Office Action does not explain what common mechanistic or other basis would lead one of ordinary skill in the art to combine them. In the absence of motivation to combine, there can be no prima facie obviousness.

Second, even if it were proper to combine these three references, they do not teach or suggest the structural differences necessary to produce Applicants' invention.

As discussed above, Neuenschwander teaches wholly distinct compounds from Applicants. For example, Neuenschwander requires a bridged bicyclic core with a nitrogen bridging atom; Neuenschwander also requires a substituted benzyloxy group in a

specific relationship to the bridged bicyclic core. This required bridged, polycyclic combination does not teach or suggest the structure of Applicant's compounds in anyway.

Furthermore, nothing in Chirgadze's R1 moieties teaches or suggests Applicants' entirely different Z' substitutions. And nothing in Connor can cure the defects of Chirgadze. Similarly, Chirgadze fails to cure the defects of Connor, namely the differences between the Applicants' invention and the required R7 moiety in Connor.

For the independently sufficient reasons stated above, Applicants respectfully request that the rejection over Connor, Neuenschwander, and Chirgadze be withdrawn.

Applicants respectfully submit that the pending claims are in condition for allowance. Applicants petition that the period for response be extended three months, up to and including September 26, 2002. Please charge any fees to deposit account number 10-0750.

Respectfully submitted,



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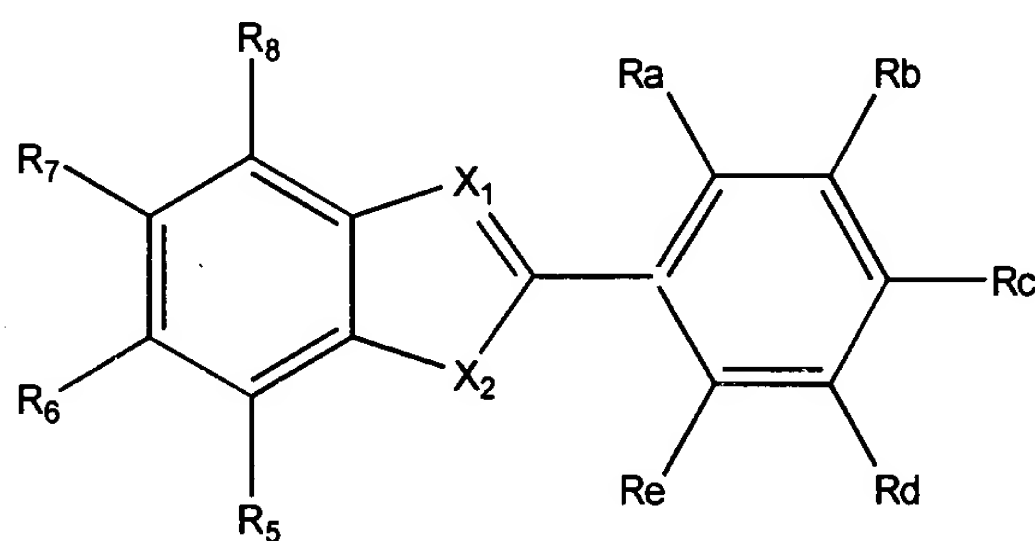
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. **(Amended)** A compound of formula (I)(B):



wherein

X<sub>1</sub> is CR<sub>1</sub>, wherein R<sub>1</sub> is H, halo, cyano, amino, or nitro; and X<sub>2</sub> is NR<sub>3</sub>;

R<sub>3</sub> is H, -SO<sub>2</sub> (C<sub>1-6</sub> alkyl), -SO<sub>2</sub> phenyl, (C=O)(C<sub>1-6</sub> alkyl), or -W'Z';

W' is a covalent bond, (C=O), SO<sub>2</sub>, or C<sub>1-6</sub> alkyl;

Z' is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkyl, phenyl, or C<sub>2-6</sub> heterocyclic radical, optionally including in the ring up to 3 additional heteroatoms or moieties independently selected from O, N, NH, S, SO, and SO<sub>2</sub>; or Z' is NR<sub>13</sub>R<sub>14</sub> where each of R<sub>13</sub> and R<sub>14</sub> is independently selected from C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, phenyl, benzyl, C<sub>3-8</sub> cycloalkyl, and C<sub>2-5</sub> heterocyclic radical;

each of R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> is independently H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo, nitro, or amino;

one of R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub>, R<sub>d</sub>, and R<sub>e</sub> is WZ and the others are independently selected from H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, halo, nitro, and amino;

W is -O-, R<sub>9</sub>, O-R<sub>9</sub>, NR<sub>10</sub>, -(CO)(O)R<sub>9</sub>, -O (CO)R<sub>9</sub>,

-(CO)NR<sub>10</sub>, or -N(R<sub>10</sub>)-CO-R<sub>9</sub>, wherein R<sub>9</sub> is C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkynylene, C<sub>2-6</sub> alkenylene, phenylene, or C<sub>2-5</sub> heterocyclic bivalent

radical, and  $R_{10}$  is H,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkynyl,  $C_{2-6}$  alkenyl, phenyl, or  $C_{2-5}$  heterocyclic radical;

Z is  $C_{2-8}$  heterocyclic radical with at least one basic nitrogen atom in the ring, optionally including in the ring up to 3 additional heteroatoms or moieties independently selected from O, C=O, N, NH, NG, S, SO, and  $SO_2$ , wherein G is  $R_{15}$ ,  $COR_{15}$ ,  $COOR_{15}$ ,  $SO_2R_{15}$ ,  $SO_2N$ ,  $CSR_{15}$ ; or Z is  $NR_{11}R_{12}$  where each of  $R_{11}$  and  $R_{12}$  is independently selected from H,  $C_{1-6}$  alkyl, phenyl, benzyl,  $C_{3-8}$  cycloalkyl, and  $C_{2-5}$  heterocyclic radical; or  $NR_{11}R_{12}$  taken together is a  $C_{6-8}$  cycloalkylimino radical; and  $R_{15}$  is  $C_{1-6}$  alkyl,  $C_{2-6}$  alkynyl,  $C_{2-6}$  alkenyl,  $C_{3-7}$  cycloalkyl, and  $C_{4-7}$  cycloalkenyl; each of the above hydrocarbyl or heterocyclic groups being optionally substituted with between 1 and 3 substituents selected from  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, halo, hydroxy, phenyl, and phenyl( $C_{1-3}$  alkyl); and wherein each of the above heterocyclic groups may be attached to the rest of the molecule by a carbon atom or a heteroatom;

provided that  $R_b$ ,  $R_d$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$ , if halo, are selected from chloro;

or a pharmaceutically acceptable salt, amide, ester, or hydrate thereof.